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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

DETAILED ACTION

The claims are not amended. The request for reconsideration has been considered but is not deemed persuasive.

Applicants' have prepared a mutual prodrug of a particular β-lactamase inhibitor sulbactam, and a list of particular β-lactam antibiotics, including cefuroxime, structured as esterifying both to the same methyl ester residue. That is, the compounds have the form A-C(O)O-CH_2-OC(O)B, where A is the stem of the sulbactam, and B is the stem of assorted cephalosporins, including cefuroxime.

The primary references teach the specific advantages of preparing a mutual prodrug by esterifying a β-lactam antibiotic and a β-lactamase inhibitor to the same methyl ester residue, albeit not with applicants' specific pair of β-lactam antibiotic and a β-lactamase inhibitor. The secondary reference teaches that specific pair, teaching that the sulbactam makes the cefuroxime more potent, and thus one is specifically motivated to use this combination. Hence the claims are obvious.

Applicants present 8 numbered points in parenthesis called the Summary, followed by a section called "Baltzer et al. v. Xiong et al. (2004)" with points 1 to 3, followed by Enqlish et al. v. Xiong et al. (2004), which has points 4-9, followed by General Arguments, which are points 10-14 There is no general correspondence between the summary points (1)-(8) and the second set of 1-24 that the examiner can determine. The examiner will respond following the latter structure.

In discussing Baltzer et al. in view of Xiong et al., points 1-2 just report the examiner's position. Applicants in point 3 state "Applicants respectfully disagree that an

artisan would extrapolate from the two penicillin-type prodrug examples presented by Baltzer et al. and assume that all β-lactam antibiotics and all β-lactamase inhibitors (a) could be combined in a single molecule, (b) would function as a pro-drug, and (c) would have advantages over a simple combination." But the examiner does not need to do anything that ambitious. The examiner does not need to "extrapolate" anything, because Baltzer teaches the concept of a mutual prodrug of β-lactam antibiotics and β-lactamase inhibitors --- that concept is even in the title. Second, no one needs to "extrapolate" that the compound would be a prodrug because, again, the reference teaches this explicitly. See the title. See the very first sentence of the Abstract, which refers to "The principle of combining a β-lactam antibiotic with a β-lactamase inhibitor in a single molecule functioning as pro-drug for the two active components". Third, no one would need to "extrapolate" the advantages because the reference teaches them explicitly. See the last line of the abstract specifically. Specifically, the paragraph bridging pages 1183-1184, says that "both the antibiotic and the inhibitor are present simultaneously in appropriate balance at the site of the infection. This will not usually be the case when the two compounds are given as a combination .... because each drug in a combination will have its own individual profile with respect to rate of absorption, distribution and duration of action." This established that one of ordinary skill in the art would be well motivated to prepare the mutual prodrug rather than the combination of β-lactam antibiotic and β-lactamase inhibitor, because the advantage to doing this is taught.

All of this the examiner has pointed out before. Applicants' analysis refuses to deal with the specific teachings of Baltzer. The reference teaches explicitly the advantage of "combining a β-lactam antibiotic with a β-lactamase inhibitor in a single molecule

functioning as pro-drug for the two active components", via esterifying both of them to the same methylene group. The secondary reference Xiong et al. teaches strong synergism between the β-lactamase inhibitor sulbactam and several β-lactam antibiotic, including cefuroxime, and thus it would be obvious to employ just that ester because that is what Baltzer teaches the advantage of doing.

Instead, applicants persist in viewing the references in isolation. Yes, it is true that the secondary reference does not teach prodruqs, and that Baltzer does not have applicants particular combination of sulbactam and cefuroxime, but that only means that neither reference anticipates. Similarly, pointing to Baltzer, applicants state, "The matrix of possible compounds of this genus is simple too large to reasonably encompass Applicants' mutual prodrug species, cephalosporins in combination with sulbactams, as obvious." All that means is that Baltzer by itself does not render the claims obvious, but that is not the rejection being made. Baltzer says that they "combine β-lactams and β-lactamase inhibitors in a single molecule which can function as a pro-drug for both of the active principles." The secondary reference then provides the particular β-lactam antibiotic and β-lactamase inhibitor.

Much the same applies to English et al. in view of Xiong et al., in which again, applicants argue in point 8 that neither reference, in effect, anticipates, and that English does not teach that there would be advantages. However, page 346 notes the advantage to be expected: "There are several advantages inherent to carboxyl-terminated double-ester prodrugs for oral delivery of pharmaceutical agents. The carboxyl moiety imparts improved water solubility, especially as the pH rises, as in transit from the stomach to the small intestine. It also provides improved prospects for isolation of crystalline solids as free acids

or as sodium salts, thus creating options to improve formulation of oral delivery forms. Another advantage is the formation of potentially innocuous organic diacids as by products after hydrolysis to the parent drug in vivo. Clinically, these advantages can be translated to drugs that are more efficacious, safe, and convenient to use. In summary, the acid-termination concept of ester prodrug design has provided novel and effective delivery forms for the ß-lactamase inhibitor sulbactam. Similar application to other drugs in order to improve oral bioavailability, formulation, water solubility, and simultaneous byproduct formation is suggested." The "Similar application to other drugs" would render such an approach obvious to any other drug which was already known to be synergistic with sulbactam. Again, all this was stated previously and again, applicants fail to deal in their remarks with this very specific teaching of the advantages to be reaped.

In point 10, applicants state, "it appears to Applicants that the Examiner has taken the view that because penicillins, a type of ß-lactam antibiotic, and sulbactams, a type of ß-lactamase inhibitor, have been mentioned in the prior art, ergo all mutual prodrugs - known and unknown - such as Applicants' novel mutual prodrug species, cephalosporins in combination with sulbactams, are obvious ... because the Examiner considers that one of ordinary skill in the art would be motivated to achieve them by the teaching of the prior art" and in point 12, applicants point out how broad the category of ß-lactam antibiotics is. This is not the position the examiner has taken, Nor does the examiner need to take such a position to reject these claims. The examiner does not have to say anything about "all mutual prodrugs - known and unknown". The examiner only has to teach particular combination as set forth in the claims --- not "unknown" ones. That is what the secondary reference does. It establishes that this is a known advantageous combination of ß-lactam

antibiotic, and β-lactamase inhibitor. Therefore, the examiner sees no "chilling effect" that applicants point to in point 11, because applicants are working with a known pair of β-lactam antibiotic and β-lactamase inhibitor and combining them (as a mutual prodrug) in the exact manner taught by both Baltzer and by English to be an advantage way of combining.

In point 14 and 16, applicants brush off the quoted text in English as "Mere .general comments". All teachings of a reference can be applied. The actual text is "Similar application to other drugs in order to improve oral bioavailability, formulation, water solubility, and simultaneous byproduct formation is suggested." That is an explicit statement that what they are teaching applies not just to the particular drugs that they happen to have worked with, but with other drugs as well, and is suggested for the four specific purposes named in the sentence. Applicants state: "These general comments, Applicants submit, do not rise to making obvious Applicants' compound and Applicants' discovery of its properties." Again, applicants are treating the references in isolation. The language of "Similar application to other drugs" does not itself point to cefuroxime. That is what the secondary reference provides. The indicated sentence teaches that their findings are not to be considered limited to the exact drugs that they worked with, but to others as well.

In point 17, applicants again return to the age of the primary references. Applicants have again given no explanation as to why the age of the reference matters. The examiner has cited ***In re Lechene***, 125 USPQ 396 and ***In re McCarn***, 101 USPQ 411 and applicants have presented no discussion on these decisions. The examiner must point out that the reference unsuccessfully attacked as being old in the ***McCarn*** case dated to 1873 and thus

was far older than the references applied here, and the references in ***Lechene*** were 34 and 52 years old, again, older than those here.

Applicants also point to the fact that their synthetic method employed a novel intermediate. The fact that a synthetic intermediate is novel does not make the product non-obvious. The claims are not drawn to a synthetic method, or a method of using the novel intermediate.

In 18, applicants state: "the selection of a mutual prodrug species including a β-lactam antibiotic from among a large class of β-lactam antibiotics is not prima facie obvious". And in 20 applicants refer to the "among the enormous number of possible β-lactamase inhibitors and β-lactam antibiotics." The examiner is not making an arbitrary selection. Regardless of how many β-lactam antibiotics and a β-lactamase inhibitors there are, this particular combination is taught in the secondary reference as being one in which one gets improved results. That is, it is a known pair of β-lactam antibiotic - β-lactamase inhibitor, and thus it would be obvious to use it to apply the teachings of the primary references.

In 19, applicants state, that the "cephalosporin ester compound is characterized in that the structures of the compound are composed by connecting methyl ester residue of sulbactam halomethyl ester with carboxyl residue of semi-synthetic cephalosporin". Correct. But this same overall structure of the connecting methyl ester residue exists in the primary references as well.

In 20, applicants refer to their "<u>improved</u> antibacterial effect, e.g., as presented in the Experimental results on page 21 and pages 23-24 respectively." However, the examiner analyzed in detail the data previously and concluded: "In fact, taken as a whole, the ester

was better than the combination in 6 cases, the same in 14, and worse in 12. That is more negative than positive." Applicants entire 13 page response does not devote a single sentence to dealing with this basic fact. Further, even in the permutations where the ester is better, why is that unexpected? Both primary references teach that one expects the ester to be better than the physical combination. The legal burden is on applicants to establish why their results should be considered unexpected. Simply pointing to an alleged large number does not make the results unexpected.

In 22, applicants in response to the examiner's summary of the results of Xiong applicants state, "Applicants respectfully submit that the Examiner has made a conclusion based on a wrong concept. Table 2 merely show "Results of susceptibility testing for transformants", which, as stated by Xiong et al. (2004) on page 266, under "4. Discussion", merely indicates "...the possibility of horizontal transfer of the resistance gene." Please note that therein is no indication in Xiong et al. (2004) for selection of the more precisely prescribed ß -1actamase resistance, nor any improved antibacterial effect". This is the exact same argument that applicants made previously. The examiner replied previously: "The results do mention the "possibility of horizontal transfer of the resistance gene" but that is not the aspect of the reference which the examiner relies on. The examiner relies on Table 2. This shows that the ß-lactamase inhibitor Sulbactam (an irreversible inhibitor of ß-lactamase; it binds the enzyme thus preventing it from destroying the ß-lactam antibiotic by opening its lactam ring) has a strong synergistic effect on the effectiveness of assorted ß-lactam antibiotics, which of course is the sole reason that ß-lactamase inhibitors are used. For example, for cefuroxime alone, in the testing against SHV-12, the MIC was 64 mg/l. When it was combined with the ß-lactamase inhibitor sulbactam, that number was reduced

to 2 --- the synergistic combination was 32 times more effective that with the ß-lactam cefuroxime alone, showing that sulbactam has hugely potentiated the cefuroxime. In fact, the other two ß-lactamase inhibitors clavulanic acid and tazobactam also gave very strong synergism. In the testing with CTM-M-3, the effect was even more dramatic. For cefuroxime alone, the MIC was >128 mg/l, meaning that they could not get the inhibition even at the highest concentration tested. But in combination with sulbactam, they obtained a value of 4mg/l. It did this with Cephalothin, Cefpodoxime, Cefotaxime, Ceftazidime and Ceftriaxone as well." Thus applicants statement that there "is no indication in Xiong et al. (2004) for .... any improved antibacterial effect" is simply false --- Table 2 shows precisely how strong the improved antibacterial effect is, e.g. in one case, 32-fold. Applicants in point 22 (and elsewhere for that matter) do not at all deal with this explicit teaching of the secondary reference, and in fact, present no reply at all to the examiner's analysis.

In 23, applicants point to the fact that they have different starting materials and "reaction sequences" and "different pathways". This is irrelevant for compound claims. A different synthetic method is not relevant to obviousness when the synthetic method itself is not being claimed. When the examiner said that that Baltzer et al. forms a mutual prodrug "in the exact same way applicants do", the examiner was not referring to the irrelevant synthetic techniques, but the fact that the prior art mutual prodrug and applicants' mutual prodrug are both formed by having the two drugs esterified to the same methylene group.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Mark L. Berch whose telephone number is 571-272-0663. The examiner can normally be reached on M-F 7:15 - 3:45.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on (571)272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Mark L. Berch/
Primary Examiner
Art Unit 1624

1/20/2010